Triazole derivatives useful in therapy

This invention relates to triazole derivatives useful in therapy (in particular in the treatment of fungal infections in humans and other mammals), methods for their use, formulations including them and processes for their production.

A large number of triazole antifungal compounds are known. For example, European Patent Application 0440372, Example 7, discloses (2R,3S)-2-(2,4-difluorophenyl)-3-(5-fluoro-4-pyrimidinyl)-1-(1H-1,2,4-triazol-1-yl)-butan-2-ol (also known as voriconazole) which has particularly good activity against the clinically important *Aspergillus spp* fungi. However, the compound has low solubility in aqueous media, necessitating the use of complexing agents to achieve satisfactory aqueous formulations, such as intravenous formulations. European Patent Application 0440372 suggests co-formulation with cyclodextrin derivatives to improve solubility; however, it is always desirable to keep the number of ingredients in a formulation to a minimum so as to minimize possible adverse reactions in patients.

UK Patent Application 2,128,193 discloses phosphoric acid esters for use as plant fungicides and insecticides.

Maurin *et al* [Int J Pharm, 1993, 94(1-3), 11-14] disclose α-(2,4-difluorophenyl)-α-[(1-(2-(3-pyridyl)phenylethenyl)]-1H-1,2,4-triazole-1-ethanol bismesylate, which is stated to be an antifungal agent having high solubility.

Other triazole antifungal agents are known from European Patent Application 0576201 and International Patent Application WO 97/01552.

European Patent Application 0413674 discloses formation of prodrugs of therapeutic glycosidase inhibitors by phosphorylating a free hydroxy group in the molecule. However, phosphorylation of tertiary hydroxy groups is not described.

It has now been found that triazole antifungal compounds of the type comprising a tertiary hydroxy group, including (2R,3S)-2-(2,4-difluorophenyl)-3-(5-fluoro-4-pyrimidinyl)-1-(1H-1,2,4-triazol-1-yl)-butan-2-ol, may be converted into pro-drugs having greatly enhanced solubility, but which are converted readily *in vivo* to give the desired active moiety.

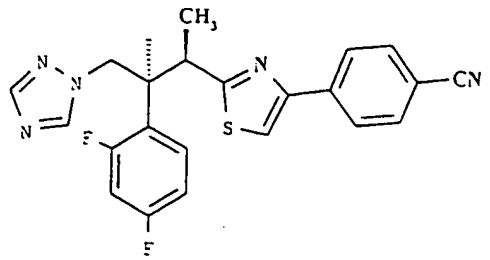
According to the invention, there is provided a compound of formula I,

$$R^1\text{-}OP(O)(OH)_2 \qquad I$$

wherein R^1 represents the non-hydroxy portion of a triazole antifungal compound of the type comprising a tertiary hydroxy group;

or a pharmaceutically acceptable salt thereof (referred to herein as "the compounds of the invention").

The compounds of the invention are distinct from the prior art because the tertiary hydroxy group in triazole antifungal compounds of this type has not previously lent itself to functionalization.



The triazole antifungal compounds corresponding to the groups (a)-(g) above are: (a) D-0870 (under development by Zeneca, see also Example 19, European Patent Application 0472392); (b) fluconazole (sold by Pfizer, see also UK Patent Application 2099818); (c) Example 7 of European Patent Application 0440372, also known as voriconazole; (d) Example 35 of US Patent No 4,952,232; (e) the compound of Example 8 of the present application; (f) Compound A of WO 95/22973 (see page 29), originally disclosed as Compound 30 in Example 27 of EP 567982; and (g) ER-30346 (see Drugs of the Future, 1996, 21(1): 20-24, Tetrahedron Letters, Vol 37, 45, pp 8117-8120, 1996 and European Patent Application 0667346, Example 88).

The present invention also provides a process for the production of a compound of formula I, as defined above, or a pharmaceutically acceptable salt thereof, which comprises phosphorylating a compound of formula II,

$$R^1OH \qquad II$$

wherein R^1 is as defined above;

and where desired or necessary converting the resulting compound into a pharmaceutically acceptable salt or *vice versa*.

The phosphorylation may be carried out using the following steps (1)-(3):

(1) Reacting a compound of formula II, as defined above, with a compound of formula III,

$$R^aR^bN\text{-}P(OR^c)(OR^d) \qquad III$$

wherein R^a and R^b independently represent $C_{1\text{-}6}$ alkyl, phenyl or substituted phenyl, or together with the nitrogen atom to which they are attached they may represent a ring such as a morpholine ring; and R^c and R^d independently represent hydroxy protecting groups selected from benzyl optionally substituted by one or more halogen atoms; to give a phosphite compound of formula IV,

$$R^1\text{-}O\text{-}P(OR^c)(OR^d) \qquad IV$$

wherein R^1, R^c and R^d are as defined above.

The reaction may be carried out in a solvent which does not adversely affect the reaction (e.g. methylene chloride) in the presence of a mild acid (for example tetrazole, 5-methyltetrazole or pyridinium hydrobromide) and optionally 4-dimethylaminopyridine, at room temperature or above.

(2) Reacting the resulting phosphite of formula IV with an oxidant (for example a peracid such as 3-chloroperoxybenzoic acid, or H_2O_2), to give a phosphate of formula V,

$$R^1\text{-}OP(O)(OR^c)(OR^d) \qquad V$$

wherein R^1, R^c and R^d are as defined above. The reaction may be carried out in a solvent which does not adversely affect the reaction (e.g. methylene chloride or ethyl acetate) below room temperature (for example 0 - -20°C).

(3) Removing the hydroxy protecting groups from the compound of formula V to give a compound of formula I, as defined above.

As an alternative to step (1), phosphites of formula IV may be prepared according to steps (1A) and (1B):

(1A) Reaction of a compound of formula II, as defined above, with PCl_3 in the presence of a base to give a postulated intermediate compound of formula VI,

$$R^1\text{-}O\text{-}PCl_2 \qquad VI$$

wherein R^1 is as defined above. The reaction may be carried out in a solvent which does not adversely affect the reaction (e.g. methylene chloride or ethyl acetate) at a temperature in the range -20 to +20°C (for example 0°C). Suitable bases include pyridine and N-methylimidazole.

(1B) Reaction of the compound of formula VI with a compound of formula R^cOH and/or R^dOH (in which R^c and R^d are as defined above) to give a compound of formula IV, as defined above. The reaction is performed without isolation of the compound of formula VI, at a temperature around room temperature.

Hydroxy protecting groups which R^c and R^d may represent include 2,6-dichlorobenzyl and 2-chloro-6-fluorobenzyl. Benzyl groups may be removed using catalytic hydrogenation (e.g. over Pearlman's catalyst or palladium-on-carbon) or bromotrimethylsilane.

If step (3) is carried out in the presence of sodium acetate or sodium hydroxide, the disodium salt may be obtained directly.

Process step (3) above, and the intermediate compounds of formula V form further aspects of the invention. Compounds of formulae II and III are either known or are available using known techniques.

It will be apparent to those skilled in the art that sensitive functional groups may need to be protected and deprotected during synthesis of a compound of the invention. This may be achieved by conventional techniques, for example as described in 'Protective Groups in Organic Synthesis' by T W Greene and P G M Wuts, John Wiley and Sons Inc, 1991.

The compounds of the invention are useful because they possess pharmacological activity in animals, including humans. In particular, the compounds are useful in the treatment or prevention of fungal infections. For example, they are useful in treating topical fungal infections in man caused by, among other organisms, species of *Candida*, *Trichophyton*, *Microsporum* or *Epidermophyton*, or in mucosal infections caused by *Candida albicans* (e.g. thrush and vaginal candidiasis). They can also be used in the treatment of systemic fungal infections caused by, for example, species of *Candida* (e.g. *Candida albicans*), *Cryptococcus neoformans*, *Aspergillus flavus*, *Aspergillus fumigatus*, *Coccidioides*, *Paracoccidiodes*, *Histoplasma* or *Blastomyces*.

Thus, according to another aspect of the invention, there is provided a method of treatment or prevention of a fungal infection which comprises administering a therapeutically effective amount of a compound of the invention to a patient. The use of the compounds of the invention as pharmaceuticals, and the use of the compounds of the invention in the manufacture of a medicament for the treatment or prevention of fungal infections are also provided.

The *in vitro* evaluation of the antifungal activities of the compounds of the invention can be performed by determining the minimum inhibitory concentration (m.i.c.), which is the concentration of the test compounds, in a suitable medium, at which growth of the particular micro-organism fails to occur. In practice, a series of agar plates, each having the test compound incorporated at a particular concentration, is inoculated with a standard culture of, for example, Candida albicans, and each plate is then incubated for

9. The use of a compound of formula I, as defined in claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prevention of fungal infections.

10. A method of treatment or prevention of fungal infections, which comprises administering a compound of formula I, as defined in claim 1, or a pharmaceutically acceptable salt thereof, to a patient in need of such treatment.

11. A process for the production of a compound of formula I, as defined in claim 1, or a pharmaceutically acceptable salt thereof, which comprises phosphorylating a compound of formula II,

$$R^1OH \qquad II$$

wherein R^1 is as defined in claim 1;

and where desired or necessary converting the resulting compound into a pharmaceutically acceptable salt or vice versa.

12. A process as claimed in claim 11, which comprises the step of removing the hydroxy protecting groups from a compound of formula V,

$$R^1\text{-}OP(O)(OR^c)(OR^d) \qquad V$$

wherein R^1 is as defined in claim 1, and R^c and R^d independently represent hydroxy protecting groups selected from benzyl optionally substituted by one or more halogen atoms.

13. A compound of formula V, as defined in claim 12.

14. A method of improving the aqueous solubility of a triazole antifungal compound of the type comprising a tertiary hydroxy group, which comprises converting the tertiary hydroxy group into an $OP(O)(OH)_2$ group, or a pharmaceutically acceptable salt thereof.